Complete Summary

GUIDELINE TITLE

Treatment of acute myeloid leukemia in older patients: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Zaretsky Y, Crump M, Haynes AE, Imrie K, Stevens A, Imrie K, Meyer RM, Hematology Disease Site Group. Treatment of acute myeloid leukemia in older patients: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Dec 18. 65 p. (Evidence-based series; no. 6-14). [68 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Newly diagnosed, previously untreated, acute myeloid leukemia (AML)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Geriatrics
Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the relative efficacy of aggressive induction chemotherapy as compared with less aggressive treatments used in the treatment of older patients (>55 years) with newly diagnosed acute myeloid leukemia (AML)
- To evaluate the optimum induction regimen for older patients with AML
- To evaluate the optimum post-remission therapy
- To evaluate the roles of granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) in conjunction with chemotherapy in this group of patients
- To evaluate what disease and patient-related parameters can be used to identify patients age >55 years who are more likely to benefit from aggressive induction therapy

TARGET POPULATION

Adult patients over the age of 55 years with newly diagnosed, previously untreated, acute myeloid leukemia (AML)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Intensive induction chemotherapy (anthracycline, anthracenedione)
2. Post-remission consolidation therapy
3. Palliative therapy (low dose cytarabine)

The following were considered but not recommended:

- Maintenance therapy for patients in first remission
- Routine use of granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjunct to intensive chemotherapy
- Use of specific prognostic factors to guide treatment

MAJOR OUTCOMES CONSIDERED

- Survival
- Response rate

- Response duration
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The MEDLINE (OVID) (1980 through February 16, 2006), EMBASE (OVID) (1980 through Week 6, 2006 [February 16]), and the Cochrane Library (2006, Issue 1) databases were searched with the term combinations shown in Appendix 1 in the original guideline document. In addition, the American Society of Clinical Oncology (ASCO) (1997 to 2005) and the American Society of Hematology (ASH) (1997 to 2005) conference proceedings were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) databases were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers for the original literature search and by one reviewer for subsequent searches. The reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Personal files were also searched.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of evidence-based guidelines, reviews, randomized controlled trials (RCTs), or meta-analyses of RCTs in newly diagnosed, previously untreated patients with acute myeloid leukemia (AML) >55 years of age. Studies that enrolled patients of all ages were also included if they contained well-described subgroup analyses according to age. The outcome measures of interest included response rate, overall survival, disease-free survival (DFS), toxicity, quality of life, and economic outcomes. During guideline development, the age of criterion for inclusion was changed from >60 years of age to >55 years of age to reflect the age of inclusion for trials evaluating elderly patients in the literature.

Exclusion Criteria

The following were not considered:

1. Studies of patients with relapsed or refractory acute myeloid leukemia
2. Studies of patients with acute promyelocytic leukemia (APL)
3. Letters and editorials

4. Articles published in a language other than English

NUMBER OF SOURCE DOCUMENTS

Nine publications were identified that met eligibility criteria. The included publications were categorized as:

1. Three full publications investigating the use of intensive versus (vs.) non-intensive induction therapy
2. Six full publications investigating the dose of induction agent
3. One abstract publication investigating palliative treatments

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Study Quality Assessment

The methodologic assessment of full report articles was examined by using the published validated quality assessment tool of Jadad et al for randomized controlled trials, but the score was not used to explicitly weight study results or to exclude studies from the analysis. The literature has shown that studies scoring ≤2 points are more likely to produce treatment effects which are on average 35% larger than those produced by trials scoring ≥3 points. Fully published articles are generally required for a confident methodological assessment, whereas because abstracts describe preliminary information with less description of the study methodology, they may provide less confidence in making treatment recommendations. Subset analyses may be useful for the generation of hypotheses but may be misleading and should not, on their own, be used to make treatment recommendations. Therefore, conclusions about the use of chemotherapy and growth factors are most influenced by the full paper publications. In addition to the Jadad scale, other study quality parameters are summarized in the original guideline document.

Synthesizing the Evidence

To determine the role of growth factors as an inducer of more rapid granulocyte recovery and primary prophylaxis of infection in the treatment of older patients with acute myeloid leukemia (AML), an aggregrate data meta-analysis was

performed pooling results of published studies, using Review Manager 4.2 (RevMan Analyses© The Cochrane Collaboration) statistical software, available through the Cochrane Collaboration. For the analyses of disease-free survival (DFS) and overall survival, the hazard ratio (HR) was used to pool the data. If the hazard ratio was not reported, it was estimated using the methods described by Parmar et al. The meta-analyses were performed using the random effects and model. Data extraction of key outcomes was performed by one reviewer and verified by a second reviewer. Intention-to-treat (all randomized patients) or evaluable (patients who were included in the analysis) data were used in the meta-analyses, according to how data were presented in the trial reports. The weighting of trials was based on the inverse variance; quality scores were not used to determine weight. The meta-analyses were performed with outcomes expressed as relative risks (RR) for dichotomous outcomes or as HRs for survival outcomes, with 95% confidence intervals (CI). The X^2 and I^2 tests were used to assess for heterogeneity of results across the trials. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. The z-test is used by Review Manager for the test of significance for treatment effect.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Quality of life and economic analyses of trials evaluating growth factors in elderly patients with acute myeloid leukemia were reviewed. Results are summarized in Table 11 of the original guideline document.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to submission of this Evidence-based Series report for external review, the report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel, which consists of two members, with expertise in

methodological issues. Key issues raised by the Panel and Disease Site Group (DSG) and responses are detailed in the original guideline document.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this Evidence-Based Series (EBS) and review and approval of the report by the PEBC Report Approval Panel, the Hematology DSG circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 82 external review participants in Ontario consisting of medical oncologists and hematologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on July 2, 2008. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology DSG reviewed the results of the survey.

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Hematology DSG and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Based on the consensus of the Hematology Disease Site Group (DSG), intensive induction chemotherapy is recommended for patients with good performance status and minimal organ dysfunction or comorbidity. Intensive induction treatment has resulted in superior outcomes (remission rates, remission duration, and survival) without an increase in toxicity, in comparison with therapy that includes reduced doses or is of palliative intent.
- Comparative data fail to demonstrate superior outcomes associated with use of a specific anthracycline or anthracenedione agent in induction. No consistent differences in treatment-related toxicities were observed. Thus, the decision as to which agent to use may be determined by other factors, such as drug acquisition costs, that may vary among institutions. For those reasons, each individual institution should determine their specific policies regarding the agent of choice.
- There is insufficient evidence to make a firm recommendation regarding the administration of consolidation therapy to older patients who have achieved a complete remission. Based on Disease Site Group consensus, it is recommended that patients in complete remission with a good performance status who have recovered from any toxicity receive at least one cycle of consolidation with conventional or intermediate dose cytarabine with or without anthracycline.

- There is no role for maintenance therapy for patients in first complete remission.
- For patients with important comorbidities who are deemed ineligible for induction chemotherapy by their physicians or whose personal preferences are for a palliative approach, treatment with low-dose cytarabine is recommended to optimize disease control while avoiding serious treatment-related toxicities.
- The routine use of myeloid growth factors (granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjunct to intensive chemotherapy in older patients with acute myeloid leukemia (AML) is not recommended.
- There is insufficient evidence to guide a recommendation on the use of specific prognostic factors to guide treatment decisions in older patients.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate treatment of older patients with acute myeloid leukemia
- Buchner et al. compared two doses of daunorubicin (60 mg/m^2 versus [vs.] 30 mg/m^2) in patients aged 60 years or older. More intensive therapy resulted in fewer early deaths and a superior remission rate, and because the duration of remission was similar in both groups, the superior remission rate in the more intensely treated patients translated into superior overall survival.
- Burnett et al. demonstrated that, in older acute myeloid leukemia patients deemed unfit for intensive chemotherapy, low-dose cytarabine was associated with higher remission rates and longer survival compared to hydroxyurea, with no difference in toxicities.

POTENTIAL HARMS

- Chemotherapy-associated toxicity
- Toxicities reported among trials evaluating anthracyclines or anthracenediones in elderly patients with acute myeloid leukemia (AML) are summarized in Appendix 2 of the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Treatment decisions in older patients with acute myeloid leukemia (AML) are complex and often influenced by comorbid illnesses, consideration of quality of life, and patient preferences. Thus, treatment recommendations described in this evidence-based series may require alteration after discussions with patients and their families.
- The Hematology Disease Site Group (DSG) recognizes that the trials reviewed for the creation of this guideline included a broad range of patients, from those where currently the use of aggressive attempts at remission might routinely be considered (e.g., those age 56-65) as well as those where only a minority of patients would be treated aggressively (e.g., those age 66 or greater). In the absence of significant weight of evidence to provide recommendations specific to the latter group, the Disease Site Group concluded that patient preferences and attention to co-morbidities (physiologic age) remain important considerations in treating elderly patients with acute myeloid leukemia.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Dec 18

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Hematology Disease Site Group (DSG) were asked to disclose potential conflicts of interest relating to the topic of this systematic review.

No conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on August 28, 2009.

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